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EXAMINER

GAKH, YELENA G

ART UNIT

PAPER NUMBER

1797

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DELIVERY MODE

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/765,718	Applicant(s) ISMAGILOV ET AL.	
	Examiner Yelena G. Gakh, Ph.D.	Art Unit 1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 January 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-7, 9-15, 17, 19, 21-34, 36, 38-44, 49-62 and 75-77 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-7, 9-15, 17, 19, 21-34, 36, 38-44, 49-62, and 75-77 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Amendment filed 01/11/08 is acknowledged. Claims 1-7, 9-15, 17, 19, 21-34, 36, 38-44, 49-62, and 75-77 are pending in the application.

Response to Amendment

2. The examiner modifies rejection of the pending claims in view of the amendment.

Claim Objections

3. Claim 6 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The limitation "solvent transfer" appears to recite an inherent feature of the method and therefore does not further limit the subject matter of the parent claim.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-7, 9-15, 17, 19, 21-34, 36, 38-44, 49-62, and 75-77 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method utilizing the carrier fluid immiscible with three plug-fluids and which comprises a step of mixing all three plug-fluids before they enter the channel, does not reasonably provide enablement for the method, which utilizes the carrier fluid, which is miscible with the three plug-fluids, and which does not comprise the step of mixing all three plug-fluids before they enter the channel. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. If the carrier fluid is miscible with three plug-fluids, the plug-fluids will not form plugs, and if there is no step of mixing all three plug-fluids before they enter the channel which is filled with the carrier-fluid, they

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will not be able to mix with each, since the formed plugs will be separated with the immiscible carrier-fluid.

Claim 3 and dependent claims are enabled only if one or more first plug-fluids comprise a precipitant and a crystallization target - in the opposite case there is no way for a routineer in the art to obtain a plug of the first plug type comprising a precipitant and a crystallization target; the same is true for the second plug-fluids.

Claims 27-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification does not disclose and does not provide any guidance for measuring and regulating osmotic pressure within the plugs, which results in undue experimentation for a routineer in the art to perform the method recited in claims 27-30, since it is totally unclear, as to how it is possible to measure, control and regulate osmotic pressure in different plugs formed by the plug-fluids.

Claims 31-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification is silent regarding regulating the ratio of plugs of two types as recited in claims 31-33, which results in an undue experimentation for a person of ordinary skill in the art to perform the method recited in claims 31-33.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-7, 9-15, 17, 19, 21-34, 36, 38-44, 49-62 and 75-77 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

While the carrier-fluid is defined in the specification as the fluid immiscible with any of the plug-fluids, the examiner suggests the Applicants to introduce the definition

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“immiscible” for the carrier-fluid in the body of the claims in order to clearly define, as to how plugs are formed from the plug-fluids, without the necessity of referring to the specification. This does not narrow the scope of the claims, since the specification provides exactly such definition for the carrier-fluid.

The recitation of claim 1 is not totally clear. It is not apparent, as to what is called "a plug-forming region of the first channel" - is this a special region which is different in its structure from the rest of the channel? Is it designed to facilitate forming the plug? It is also not clear, how pressure applied to plug-fluids can cause formation of the plugs? It appears from the specification that formation of plugs is caused by introducing the plug-fluids into immiscible carrier-fluid. However, nothing like this is recited in the claim, which renders the claim unclear and indefinite. Also, it is not quite clear, which solvent is meant for the second plug-fluid, which comprises water? Is this an additional solvent?

Claim 2 is not apparent, as to how additional plug-fluids recited in the claims are related to the method recited in the parent claim, since the crystallization already took place for the plug-fluids recited in claim 1? If claim 2 was meant to recite additional plug-fluids for modifying conditions of crystallization, the examiner suggests the Applicants to reconsider the language of the claim, since it is not what is recited in the presently pending claim.

From claim 3 it is not apparent, as to how the crystallization is prevented in the plug of the first plug type, which comprises both the precipitant and crystallization target? Further, claim 3 is confusing as to which specific embodiment it recites, with a plurality of combinations of introducing plugs of the first and second type in different plug-forming regions of the first and second channel. Furthermore, it is not apparent, as to what is the difference between the first, the second and the third plug-forming regions, and where these regions are located - in both channels, in one of the channels? Claim 3 is unclear and indefinite.

Claim 6 is not apparent, as to how the solvent can be transferred from one plug into another, if the plugs are separated by the carrier fluid immiscible with the solvents of the plugs? It is also not clear, if “a solvent” of claim 6 is anyhow related to “a solvent” of the parent claims? If it is the same solvent, the article “the” should be used instead. If

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the solvent is miscible with the carrier-fluid, then it inherently transfers into it, and this is not an active step of the method.

It is not apparent, as to what the difference between the first and the second plug-forming regions is, and therefore it is not clear, as to what is the difference between recitations of claims 9 and 10.

Claim 13 is confusing. Which specifically plug-forming region out of three is meant in the claim? Also, how the second carrier fluid can separate plugs, which are already introduced into the first channel?

Claim 15 recites introducing the carrier-fluid into the substrate - this appears to be different from introducing the fluids into the channels of the substrate of the parent claims. The examiner suggests rewriting the claim as reciting "into the channel(s)".

Examiner's Note. In order to provide antecedent basis for the limitations in all dependent claims, indefinite article "a" should be replaced with "the" in all claims, where appropriate.

Claim 23 recites the limitation for mixing, which is not mentioned in the parent claims, and which therefore lacks antecedent basis.

Claim 24 has the same problem as claim 15 regarding reciting introducing the carrier-fluids and plug-fluids into the substrate rather than into the channel. This makes it unclear, as to whether this is a different set-up from what was disclosed in the parent claim. Besides, the subject matter of claim 24 is very confusing. How is it possible that "the concentration of a first component in the plug of one plug-type provides a correlative and quantitative measure of a second component in an adjacent plug"? What one has to do with the other? The recitation does not seem to be meaningful.

It is not clear from claim 25, how "a marker" is related to the precipitant or the crystallization target, which are the major components of the plugs? It is the marker for what?

It is unclear from claim 26, which plug-fluid comprises a salt, since a salt can be a co-precipitant, and also it is not clear, how the plug with the crystallization target can comprise the salt?

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Claims 27-30 recite controlling and regulating osmotic pressure in the plug. It is not apparent, as to how the osmotic pressure in the plugs is measured, controlled and regulated.

Claims 40-41 seems to contradict the definition of the "carrier fluid" provided in the specification, which is supposed to be immiscible with the plug-fluids, at least one of which comprises water. Moreover, the term "permeable" is usually related to solids being permeable to gases and liquids, rather than to the liquids. For the liquids the conventional term is "miscible". It is not apparent, as to how one liquid can be "permeable" to another liquid.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

9. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
 2. Ascertaining the differences between the prior art and the claims at issue.
 3. Resolving the level of ordinary skill in the pertinent art.
 4. Considering objective evidence present in the application indicating obviousness or nonobviousness.
10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

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11. **Claims 1-7, 9-15, 17, 19, 21-22, 24-26, 36, 38-44, 51-62 and 75-77** are rejected under 35 U.S.C. 103(a) as being unpatentable over Weigl et al. (US 6,409,832) (Weigl) in view of Chayen (J. Cryst. Growth, 1999).

Weigl discloses "protein crystallization in microfluidic structures" with "a protein samples and a solvent solution combined within a microfluidic channel having laminar flow characteristics which forms diffusion zones, providing for a well defined crystallization". Weigl discusses various types of protein crystallization, and emphasizes that microfluidic crystallization is extremely efficient for diffusion-based crystallization:

"A T-Sensor-like structure, generally indicated at 10, is shown in FIG. 1 to demonstrate the principles of diffusion-based crystallization. A sample 12 containing dissolved protein, and a reagent 14 containing a variety of different solvents and salts, flow together in parallel within a channel 15 of T-Sensor 10. After establishing a laminar flow profile, the flow is significantly slowed or stopped. The various components of both streams 12, 14 will now diffuse into each other at a certain rate, depending on the size of the molecules within these streams, forming diffusion interface zones 16, 18 within channel 15 of device 10. This action establishes a concentration gradient in device 10, which allows for a very well defined crystallization. Solvent molecules from one stream can diffuse into a parallel stream containing a different solvent and particles. The change in solvent properties along diffusion interface zones 16, 18 can then induce crystallization or precipitation. Obviously, it is also possible to apply a temperature gradient to a microchannel, either across the channel or along its flow direction, and affect the precipitation characteristics this way. Microseeding would be another possibility with this device" (col. 11, lines 54-67 and col. 12, lines 1-8). The fluids are introduced with syringes (under controllable pressure) (col. 12, lines 45-67).

Weigl discloses continuous laminar flow with stopping the flow after establishing a laminar flow profile. Weigl does not specifically disclose crystallization in plugs formed by the plug-fluids comprising corresponding components (a crystallization target, a precipitant, etc.).

Chayen teaches "crystallization with oils: a new dimension in macromolecular crystal growth". In particular, Chayen discloses the following:

"A series of microbatch experiments shown in Fig. 2 demonstrates how the application of oil can determine the contact area between the trial and its supporting vessel, thereby enabling the experimenter to monitor the nucleation and reduce or increase its level at will. The Figure illustrates three situations: (a) illustrates a drop dispensed into oil as performed by the normal microbatch procedure[4]; the drop forms a spherical shape, with just a small part of it touching the floor of the container; (b) represents a drop which has been dispensed directly onto the floor of the vial and then covered by a layer of oil; the drop spreads out and flattens over the floor of the container, occupying a larger area of contact. In Fig. 2c all contact between the solution of a crystallization trial and its supporting vessel is eliminated by suspending a crystallization drop between two oils of

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different densities: one of higher and the other of lower density than that of water and the common crystallizing agents. The two oils, high-density fluorinated silicone fluid (ρ 1.27 g/cm³, Merck catalogue no. 63026 2C) and low-density polydimethylsiloxane (ρ 0.92 g/cm³, Merck catalogue no. 63003 4P) are not miscible and the drop, which has a density value between those of the two oils, floats at the interface thereby not touching the container walls [24,25]. *The number of carboxypeptidase G2 (CG2) crystals produced by procedures (a) and (c) is significantly reduced and their size is larger (Fig. 2d) compared with those grown by procedure (b) where the drop has the largest contact area with its vessel (Fig. 3e).* Similar results have been obtained with thaumatin, lysozyme [24,25] and apocrustacyanin C2 [24]" (page 437, right column, page 438, left column).

Thus, Chayen demonstrates advantages of controlling crystallization in a microdroplet suspended in the oil.

It would have been obvious for a person of ordinary skill in the art to modify Weigl's method of crystallization in microfluidic structures by performing crystallization in plugs instead of during stop-flow, because Chayen expressly demonstrates preferences of microbatch crystallization in droplets suspended in oil, which are similar to plugs separated by an immiscible carrier fluid in microfluidic channels. It would have been obvious to have various plug-fluids comprising different components required for performing crystallization in order to form plugs with different composition and obtain a plurality of crystallization conditions for further high-throughput screening; it would have been obvious for a routinier in the art to analyze crystals either directly from the microchannels or by transferring the crystals into conventional vials used for crystallographic analysis, such as X-ray analysis.

Such embodiments as obtaining different concentrations of the crystallization components for high-throughput analysis is well known in the art, with an obvious modification of the instant method by varying the pressure and the flow rates of the plug-fluids.

12. **Claim 23** is rejected under 35 U.S.C. 103(a) as being unpatentable over Weigl in view of Chayen, as applied to claims 1-7, 9-15, 17, 19, 21-22, 24-26, 36, 38-44, 51-62 and 75-77 above, and further in view of Bardell et al. (US 2001/0048900 A1) (Bardell).

While Weigl in view of Chayen do not specifically disclose turn in a channel for increasing mixing in the channel, Bardell discloses specifically such turns in channels for increasing mixing of the fluids in the channels, which makes it obvious for a person of

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ordinary skill in the art to modify Weigl -Chayen's method by introducing turns in channels for increasing the mixing within the plugs.

13. **Claims 49-50** are rejected under 35 U.S.C. 103(a) as being unpatentable over Weigl in view of Chayen, as applied to claims 1-7, 9-15, 17, 19, 21-22, 24-26, 36, 38-44, 51-62 and 75-77 above, and further in view of Pantoliano et al. (US 6,569,631) (Pantoliano).

While Weigl in view of Chayen do not specifically disclose fluorescent marker within one of the plug-fluids, using fluorescent markers for monitoring crystallization of e.g. proteins is disclosed by Pantoliano, which makes it obvious for a person of ordinary skill in the art to utilize this feature for crystallization monitoring in Weigl-Chayen's method.

Response to Arguments

14. Applicant's arguments filed 01/11/08 have been fully considered but they are not persuasive. The examiner does not think that the Applicants adequately addressed all rejections of the pending claims under 112, first and second paragraphs. The examiner respectfully suggests the Applicants to look through all issues of enablement and unclarity raised by the examiner in the previous and present Office actions in order to accelerate the prosecution of the case. The Applicants again state in their arguments that it is pressure applied to the plug-fluids that causes formation of plugs. The examiner does not understand this statement. How pressure can cause the plug-fluids form the plugs? Isn't this the immiscible carrier-fluid, which causes formation of plugs upon introducing the plug-fluids into the carrier fluid?

Regarding claim 2, in order to make the recitation of the claim and the sequence of the steps clearer, it should be indicated that the steps recited in claim 2 occur before the step of crystallization recited in claim 1 takes place.

Regarding claim 6, first, the word "permeability" does not seem to be a correct term for defining a diffusion of one liquid into another liquid. Also, according to the specification the plug-fluids are immiscible with the carrier-fluid (see the Summary of the

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Invention), and the third plug-fluid comprises water. This contradicts the recitation of claim 6. The same is true for claims 40 and 41.

There are many more unclarity issues than just those addressed by the Applicants in their Remarks. The examiner respectfully requests the Applicants to respond to all of them to make the subject matter of claims clear either by their amendment or by the explanation of what the claims in fact recite.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yelena G. Gakh, Ph.D. whose telephone number is (571) 272-1257. The examiner can normally be reached on 9:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill A. Warden can be reached on (571) 272-1267. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Yelena G. Gakh/
Primary Examiner, Art Unit 1797

3/16/2008